Psychiatry Research: Neuroimaging 214 (2013) 56–65

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

A developmental study on the neural circuitry mediating response flexibility in bipolar disorder

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ARTICLE INFO

Article history:
Received 21 May 2012
Received in revised form
9 April 2013
Accepted 17 May 2013

Keywords:
Bipolar disorder
Neuroimaging
Response flexibility
Cross-sectional
Stop-change task

ABSTRACT

Cross-sectional neuroimaging studies are an important first step in examining developmental differences in brain function between adults and youth with bipolar disorder (BD). Impaired response flexibility may contribute to reduced ability to modify goal-directed behavior in BD appropriately. We compared neural circuitry mediating this process in child (CBD) vs. adult BD (ABD) and age-matched healthy subjects. fMRI data from 15 CBD, 23 ABD, 20 healthy children, and 27 healthy adults were acquired during a response flexibility paradigm, a task where subjects inhibit a prepotent response and execute an alternative response. When successfully executing an alternate response, CBD showed frontal, parietal, and temporal hyperactivation relative to healthy children and ABD, while ABD hypoactivated these regions relative to healthy adults. Previous studies of response flexibility in healthy volunteers revealed frontal, temporal, and parietal cortex hyperactivation in children and hypoactivation in adults. Relative to age-matched healthy subjects, we found hyperactivation in these regions in CBD and hypoactivation in ABD. This suggests that our findings in patients may represent the extreme extension of the age-related response flexibility activation differences found in healthy subjects. Future studies should use longitudinal fMRI to examine the developmental trajectory of the neural circuitry mediating response flexibility in BD.

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1. Introduction

Developmental studies in bipolar disorder (BD) can inform future treatment and prevention efforts (National Institute of Mental Health Strategic Plan, 2010). Specifically, cross-sectional comparisons of neural activity in youth vs. adults with and without BD can help determine the extent of shared pathophysiology in early- and later-onset BD. Examining the pathophysiological differences between child and adult BD adds to existing literature showing smaller amygdala volume in early- vs. late-onset illness (Blumberg et al., 2003; Chang et al., 2005), and may help explain developmental differences in clinical course, with earlier age of onset associated with higher rates of comorbid disorders and number of recurrences, and shorter periods of euthymia (Perlis, 2004; Birmaher, 2007). A previous functional magnetic resonance (fMRI) study found evidence of age- and BD-related frontal dysfunction during unsuccessful motor inhibition. Compared with age-matched comparison subjects, children with BD (CBD) showed anterior cingulate cortex (ACC) hypoactivation, while adults with BD (ABD) showed ACC hyperactivation (Weathers et al., 2012). Response flexibility is a cognitive function closely related to motor inhibition, since successful response flexibility depends, in part, on the ability to inhibit prepotent motor responses in the presence of behaviorally salient cues. Studies of the neural mechanisms mediating response flexibility are particularly relevant in BD because BD patients show reduced ability to modify their behavior in response to environmental cues e.g., anhedonic depressed subjects who do not pursue rewarding goals, or manic patients who pursue unrealistic goals. However, no study has compared neural activity in adults and youth with BD during response flexibility. The goal of this study was to use a response flexibility task to compare brain activation in CBD, ABD, and age-matched healthy subjects, when subjects were confronted with changing behavioral demands.

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0925-4927/$ - see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.pscychresns.2013.05.002

Response flexibility is an executive function that resembles simple motor inhibition in that both depend on sustained attention and the inhibition of prepotent responses (Swann et al., 2003; Pavuluri et al., 2010). However, response flexibility differs from motor inhibition in that only the former requires subjects to execute an alternative response when the appropriate cue appears. Behavioral data on a response flexibility task indicate that BD youth are slower than healthy subjects at substituting a prepotent response ("go") with an alternate response ("change") (McClure et al., 2005), and thus have impaired response flexibility. While no study has used a response flexibility task in ABD, data indicate that BD adults are impaired in psychological domains related to response flexibility, such as attention shifting (Iverson et al., 2009) and motor inhibition (Bora et al., 2009).

In healthy subjects, executing the alternate response successfully during response flexibility engages brain regions mediating inhibition, cognitive control, sustained attention, and signal detection (Bunge et al., 2002; Rubia et al., 2007b; Thomas et al., 2011). Studies suggest that response flexibility improves with age, with healthy adults showing faster response times to change signals than healthy children (Thomas et al., 2011). Further, regions mediating processes involved in response flexibility show more widespread cortical engagement in healthy youth than adults, including (1) inferior frontal cortex (IFC) during motor inhibition; (2) insula cortex during cognitive control; (3) precuneus and inferior parietal cortex during sustained attention; and (4) middle frontal gyrus and temporal cortex during signal detection (Bunge et al., 2002; Rubia et al., 2007b; Thomas et al., 2011; Carp et al., 2012).

Neuroimaging studies have revealed abnormal brain activation in BD children vs. healthy children, and BD adults relative to healthy adults, during response flexibility and related tasks (Passarotti et al., 2010; Singh et al., 2010). Some of these studies report that, relative to healthy subjects, patients show hyperactivation, while other studies report hypoactivation in patients. This disparity in findings may be due to the differences in tasks across studies. For instance, in an fMRI study using the response flexibility task, CBD compared to child healthy subjects showed middle frontal gyrus, insula, and precuneus hyperactivation during successful change vs. go trials (Nelson et al., 2007). While no fMRI study has tested response flexibility in ABD, middle temporal gyrus, precuneus, and inferior frontal gyrus hypoactivation occur during response inhibition in ABD vs. healthy subjects (Strakowski et al., 2008; Mazzola-Pomietto et al., 2009). Furthermore, during unsuccessful response inhibition, CBD showed increased ACC activation, whereas adult ABD showed decreased activation, relative to healthy subjects (Weathers et al., 2012). Since inhibition of prepotent responses is a core component of response flexibility (Kenner et al., 2010), these data suggest that ABD may also exhibit neural dysfunction during response flexibility.

Using event-related fMRI, we compared adults and youth with BD and age-matched healthy subjects on neural function during successful and unsuccessful change trials. As noted above, existing literature shows (1) improved response flexibility in adult vs. child healthy subjects (Thomas et al., 2011); (2) increased precuneus, middle frontal gyrus, insula cortex and IFC activation in healthy adults vs. healthy children during successful response flexibility and cognitive control (Bunge et al., 2002; Thomas et al., 2011); (3) middle frontal gyrus, insula, and precuneus hyperactivation in CBD vs. child healthy subjects during successful change trials (Nelson et al., 2007); and (4) IFC hypoactivation in ABD vs. healthy adults during response inhibition (Mazzola-Pomietto et al., 2009). Finally, clinical studies have shown that earlier age of onset of BD is associated with higher rates of comorbid illness, more recurrences, and shorter periods of euthymia (Perlis, 2004; Birmaher, 2007). Based on these findings, we hypothesize that, compared to age-matched healthy subjects, BD patients will show hyperactivation of middle frontal, precuneus, insula, and inferior frontal regions during successful response flexibility, and that this dysfunction will be present in more cortical regions in BD youth than in BD adults.

2. Methods

2.1. Participants

Participants were part of an ongoing IRB-approved study at the National Institute of Mental Health. Adult subjects and parents/guardians of child subjects provided informed consent; children provided informed assent.

We recruited BD patients via advertisements to support groups and clinicians. Patients in all mood states (euthymic, depressed, and hypo/manic), as well as both medicated and unmedicated BD patients were included in the study. Community participants (20 healthy children and 27 healthy adults) were recruited from the community through advertisements. They had no lifetime psychiatric diagnoses or first-degree relatives with a mood or anxiety disorder. Exclusion criteria in all groups were: I.Q. < 70, substance abuse within the past 3 months, major medical illnesses, neurological damage/disorder, comorbid attention deficit hyperactivity disorder, and pervasive developmental disorders. No participants were related.

Children were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (Kaufman et al., 1997) by master's or doctoral level clinicians with excellent interrater reliability ($\kappa > 0.9$ for all diagnoses). Child BD participants ($N=15$) met criteria for "narrow phenotype" BD, i.e., having experienced at least one hypomanic (≥4 days) or manic (≥7 days) episode characterized by abnormally elevated mood or grandiosity, and at least three criterion "B" mania symptoms (Leibenluft et al., 2003). Pediatric BD included both BD-I ($N=12$; 80%) and BD-II ($N=3$; 20%) (Table 2). The inclusion criterion for adult patients was a diagnosis of BD-I or BD-II using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (First et al., 2002) or the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). The ABD group ($N=23$) consisted of BD-I ($N=14$; 60.9%) and BD-II ($N=9$; 39.1%) patients (Table 2). Age at onset of BD illness was computed as the chronological age at the time of first manic or hypomanic episode.

Within 48 h of scanning, mood was assessed for pediatric patients using the Children's Depression Rating Scale (CDRS) (Poznanski et al., 1984) and the Young Mania Rating Scale (YMRS) (Young et al., 1978), and for adult patients using the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD) (Williams et al., 1988) and YMRS (data missing for two adult patients).

Of the 153 individuals scanned, data were excluded for 68 (44.4%): 19.6% (30/153) for excessive movement (>3 mm in any direction) [12 CBD, 9 child healthy subjects, 3 adult healthy subjects, 6 ABD], 15.7% (24/153) for poor performance (go trial accuracy $<65\%$) [10 CBD; 6 child healthy subjects; 4 adult healthy subjects; 4 ABD], 7.1% (11/153) for equipment failure [3 CBD; 5 child healthy subjects, 2 adult healthy subjects, 1 ABD], and 2.0% (3/153) for abnormal clinical findings [2 child healthy subjects; 1 adult healthy subject]. Included vs. excluded patients did not differ in YMRS, CDRS, or SIGH-SAD scores, or proportion in euthymic, hypomanic, depressed, or mixed states (all $Ps > 0.05$). The final sample ($N=85$) includes 15 CBD, 20 healthy children, and 27 healthy adults, who have been included in previous reports (Nelson et al., 2007; Thomas et al., 2011). None of the data on this task from the $N=23$ ABD have been reported in previous studies.

2.2. Design and procedure

The paradigm used in this study has been described in detail elsewhere (McClure et al., 2005; Nelson et al., 2007; Thomas et al., 2011), and is an adaptation of the stop-signal paradigm (Logan et al., 1997). Briefly, at the start of each trial a white fixation cross appeared at the screen center for 500 ms. This was replaced by an "X" or "O" "go signal" for 1000 ms. Using a button-box, subjects were instructed to press "1" for "X" and "2" for "O". Participants were told to respond within 1000 ms, unless the change signal appeared (i.e., background changed to blue) when they were instructed to press "3".

On the first change trial, the change signal appeared 250 ms after the g-signal. Subsequent change-signal timing was adjusted on a trial-by-trial basis based on subject performance. If the subject changed successfully, the next change signal appeared 50 ms later than on the last change trial; if the subject failed, the signal appeared 50 ms earlier than on the last change trial leading to an approximate change accuracy rate of 50%. Participants did not receive feedback on their performance during the task. To examine brain activation associated with each trial, jitter was introduced by randomly inserted fixation trials lasting 750 ms.

Before scanning, subjects were trained to a mean reaction time (RT) less than 1000 ms on "go" trials. To ensure the prepotency of the go response, there were more go trials ($N=176$) than change trials ($N=80$) while scanning. Therefore, the "go" response is the prepotent response, and the less common "3" button press to